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(54) HOLLOW FIBER MEMBRANE

(57)Abstract:
PROBLEM TO BE SOLVED: To provide hollow fiber membrane which is capable of reducing such risk that anaphylaxis response or pyrexia during dialysis is caused, and also has excellent properties with respect to assembling of the membrane hollow fibers into a membrane module.
SOLUTION: This hollow fiber membrane substantially consists of a polysulfone-based polymer and polyvinylpyrrolidone, wherein the correlation of the polyvinylpyrrolidone content (Ci) in the inner surface of the membrane with the polyvinylpyrrolidone content (Co) in the outer surface of the membrane and the average polyvinylpyrrolidone content (Cave) inside the membrane, is represented by the following relational expressions: $Ci \geq Co \times 3$; and $Ci \geq Cave \times 2$.

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CLAIMS

[Claim(s)]
[Claim 1] The hollow fiber which is film which consists of a polysulfone system polymer and a polyvinyl pyrrolidone substantially, and is characterized by expressing the relation of the polyvinyl-pyrrolidone content (Ci) of a film internal surface, the polyvinyl-pyrrolidone content (Co) of a film outside surface, and the average polyvinyl-pyrrolidone content (Cave) in the film with a bottom type.
Ci>=Cox3 and Ci>=Cavex2 -- [Claim 2] The hollow fiber according to claim 1 whose membranous endotoxin adsorption capacity force is two or more 2000 EU/m.
[Claim 3] The hole density of a film outside surface is 25%. Hollow fiber according to claim 1 or 2 which it is above.
[Claim 4] The hollow fiber according to claim 1 to 4 in which it obtains and deals by washing this hollow fiber 30 seconds or more in hot water 80 degrees C or more after water 40 degrees C or more washes 1 minute or more in a spinning process.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to a new hollow fiber. There is little generating of an anaphylactic reaction, it is the film used for the therapy of renal failure etc. in detail, since mixing of endotoxin can be prevented by adsorption, safety is high, and it is related with the blood purification film excellent in module-assembly nature.
[0002]
[Description of the Prior Art] Most uses a polyvinyl pyrrolidone (PVP) for the blood purification film which uses a polysulfone system polymer as a raw material as a membranous hydrophilization agent. Since hydrophilization of the film will be carried out if PVP is used, adsorption of the plasma protein to a film surface can be controlled, a membranous fractionation property improves, and the engine performance as blood purification film improves. The approach of putting in PVP in the film has the common approach of causing phase separation and making carry out film formation by sending out the liquid within freezing characteristic from inner liquid at the same time it dissolves a polymer and PVP in a common solvent, and adds a non-solvent depending on the case, it considers as a spinning undiluted solution and it carries out the regurgitation from a nozzle, and shutting up PVP in the film.
[0003] However, although PVP which exists in a Polymer-rich phase in phase separation is in a polymer and a compatible condition within a polymer, PVP in a Polymer-lean phase turns into free PVP after coagulation. Free PVP has the danger of it being eluted into blood and causing an anaphylactic reaction at the time of blood contact. And although the polysulfone system polymer has the property of adsorbing endotoxin properly speaking, it is adding and carrying out hydrophilization of PVP, and an adsorption property is lost, mixing of endotoxin is seen and the case where a dialysis patient becomes feverish can see. There is also a report that an anaphylactic reaction arises because the elution of PVP and mixing of endotoxin take place to coincidence depending on the case, and the elution of PVP and mixing of endotoxin are the technical problems which should be avoided absolutely.

[0004] Moreover, since PVP eluted on the membranous outside intervenes, yarn adheres (fixing) and adhesion resin does not permeate the gap of yarn, when drying the film, when a bundle is used as a module, leak arises. Moreover, even if this module manufacture is possible, since a fixing part does not serve as a membranous effective area, it is inferior to the solute removal engine performance. In order to prevent fixing, the approach of twisting spacer yarn around yarn is also adopted, but while it is the process which requires time and effort very much, cost starts.
[0005] Thus, although a PVP's in film existence condition is a very important problem and PVP is the required matter in the field of an engine-performance manifestation, that the endotoxin adsorption capacity force is lost while becoming the cause of an anaphylactic reaction or fixing, if there is much free PVP poses a problem common to a polysulfone system hollow fiber.
[0006]
[Problem(s) to be Solved by the Invention] The hollow fiber excellent in module-assembly nature is obtained at the same time it reduces the danger of generation of heat under an anaphylactic reaction and dialysis.
[0007]

[Means for Solving the Problem] This inventions are as follows.
** The hollow fiber which is film which consists of a polysulfone system polymer and a polyvinyl pyrrolidone substantially, and is characterized by expressing the relation of the polyvinyl-pyrrolidone content (Ci) of a film internal surface, the polyvinyl-pyrrolidone content (Co) of a film outside surface, and the average polyvinyl-pyrrolidone content (Cave) in the film with a bottom type.
The hollow fiber given [above-mentioned] in ** the given endotoxin adsorption capacity force of Ci>=Cox3 and the Ci>=Cavex2 ** film is two or more 2000 EU/m.
** The hole density of a film outside surface is 25%. Hollow fiber the above-mentioned ** which it is above, or given in **.
** A hollow fiber given in either the above-mentioned ** manufactured by the spinning approach that more than air gap residence-time 0.5 second, the coagulation bath temperature of 70 degrees C or more, and nozzle temperature are lower than coagulation bath temperature 20 degrees C or more thru/or **.
** A hollow fiber given in either the above-mentioned ** obtained by washing this hollow fiber 30 seconds or more in hot water 80 degrees C or more after water 40 degrees C or more washes 1 minute or more in a spinning process thru/or **.
[0008]
[Embodiment of the Invention] The blood purification film in this invention consists of a polysulfone system polymer and a polyvinyl pyrrolidone (PVP) substantially. A polysulfone system polymer is a film material which is excellent in biocompatibility and a membranous fractionation property. Also in a polysulfone system polymer, polyether sulphone (PES) is desirable as a material of the field of biocompatibility and thermal resistance to the hemodialysis film. When using a polysulfone system polymer for the hemodialysis film, in order to control adhesion on the film of a plasma protein, PVP is used as a membranous hydrophilization agent in many cases. The ability as hemodialysis film can be demonstrated because include PVP in the film and it carries out hydrophilization.
[0009] However, when PVP is eluted from the film and goes into a dialysis patient's blood, there is a danger of triggering an anaphylactic shock reaction. Moreover, it is placed between the gaps of yarn by PVP eluted on the membranous outside, and yarn adheres (fixing of yarn). In the case of a module assembly, adhesion resin does not infiltrate into the gap of yarn, but, as for the bundle which fixed, leak takes place. That is, although PVP is very important in respect of an engine-performance manifestation, PVP beyond the need has a problem in respect of safety or module-assembly nature. Although especially PVP held in the blood contact surface at the film is indispensable in order to discover solute permeability ability, there is no semantics in which PVP exists in other film supporters parts.
[0010] Moreover, it is known that there is endotoxin adsorption capacity in a polysulfone system polymer. If PVP exists in a membranous supporters part mostly, endotoxin adsorption capacity will be spoiled by the hydrophilization effectiveness of PVP. There is also a report that the synergistic effect with PVP to which the patient was eluted in generation of heat when the endotoxin which exists in dialysing fluid entered into blood through the film triggers an anaphylactic shock reaction. Although each dialysis facility is tackling defecation of dialysing fluid, it is impossible to obtain dialysing fluid without endotoxin as a matter of fact. Then, if the endotoxin adsorption capacity force is in the film, endotoxin can prevent entering into a patient's blood. Therefore, it is better not to exist in other parts, although PVP is required for the blood contact surface absolutely.
[0011] Although how to fix to a hollow filament inside can be considered after carrying out spinning of the hollow filament if it is going to make PVP exist only in the blood contact surface, it is very difficult the field of cost, and in respect of being technical. Therefore, a polymer and PVP are supplied in the spinning undiluted solution, and the approach which the inside of the hollow filament which is the blood contact surface is made to localize in a spinning process is effective.
[0012] The hollow fiber in this invention extrudes the spinning undiluted solution which consists of a polymer, a non-solvent, PVP, and a solvent from the outside of a duplex spinneret, and after it is immersed to a coagulation bath through discharge and the air gap section, it can rinse and obtain a freezing characteristic liquid from the inside. Phase separation begins the extruded spinning undiluted solution with the liquid within freezing characteristic. PVP which exists in the Polymer-rich phase in phase separation is in a polymer and a compatible condition within a polymer, and after coagulation is

not eluted into blood, even if it is shut up in a polymer and the film contacts blood. However, PVP in a Polymer-lean phase is free, and it is necessary to flush it in the wash bath in a spinning process. As a result of flushing free PVP, PVP localizes to the compact layer of the blood contact surface, and the film with the low content of PVP is obtained by the membranous supporters part.

[0013] The relation between PVP content [on the content of PVP to 1 H-NMR and the polysulfone system polymer called for from a surface infrared absorption spectrum and as opposed to the polymer of a film internal surface] (Ci), and the PVP content (Co) of a film outside surface and the average PVP content (Cave) in the film is Ci>=Cox3 and Ci>=Cavex2. (formula 1)

At the time of **, PVP is concentrating on the film internal surface which is the blood contact surface, the PVP content of a supporters part becomes low, and it is desirable.

[0014] Although it is the approach of fully flushing free PVP, it is inadequate just to merely strengthen washing. The most important thing is making an outside surface puncture greatly in membranous structure. Washing effectiveness improves by making an outside surface puncture, and free PVP can fully be removed. When puncturing is not seen by the outside surface, PVP is prevented from free going away out of the film in the film. In that case, fixing of yarn occurs at the same time the PVP elution volume to the inside of blood increases.

[0015] 25% or more of the hole density of an outside surface is desirable. Washing effectiveness falls, and fixing of yarn generates 25% or less of case at the same time a PVP elution volume increases. The measuring method of outside-surface hole density photos the outside surface of a hollow filament sample by one 10,000 times the scale factor of this with a scanning electron microscope (SEM), copies a SEM image on the approach using an image processing system, or tracing paper, cuts off a puncturing part, and has a method of measuring and finding the weight of paper. Quantum nature has the highly desirable approach of searching for by the image processing also in it. It is desirable to use the image processing system image analyzer V20 by Toyobo Co., Ltd. as an approach of searching for by the image processing. By the TOKS method automatic binarization method, an aperture is made into white, others are made black, and it considers as outside-surface hole density in quest of the ratio of the area of a white part, and the whole area.

[0016] A means to gather the hole density of an outside surface lengthens AG die length in a dryness-and-moisture type spinning method, or it is effective to reduce spinning speed. That is, it is long and the residence time of the AG section is made into 0.5 seconds or more. The liquid within freezing characteristic can be made to determine membranous structure by lengthening the AG section residence time. That is, in order to avoid that a compact layer forms in an outside surface by strong coagulation from an outside surface, AG residence time is lengthened. The film is introduced to a coagulation bath, after structure is determined by inner liquid. By this approach, there is no compact layer in an outside surface, and the punctured film is obtained.

[0017] Although the film with which the outside surface punctured the residence time of the AG section by lengthening is obtained, just it is inadequate in order to gather hole density. In order to gather the hole density of an outside surface, existence of the moisture in the AG section is indispensable. The spinning undiluted solution breathed out from the duplex spinneret absorbs the steam which exists in the AG section, phase separation starts it, and the film which the outside surface punctured greatly is obtained. Specifically, outside-surface hole density can be made 25% or more by keeping the temperature of the AG section at 40 degrees C or more, and keeping humidity to 90% or more.

[0018] The concrete means which makes temperature of the AG section 40 degrees C or more, and makes humidity 90% or more has the effective approach of making coagulation bath temperature of 70 degrees C or more, and nozzle temperature lower 20 degrees C or more than coagulation bath temperature. The phase separation of an outside surface is promoted with the steam which evaporates from a coagulation bath.

[0019] After making a membranous outside surface puncture to 25% or more, it is necessary to fully wash. In a spinning process, after 40-degree C water washes washing 1 minute or more, its approach of washing 30 seconds or more in 80-degree C hot water is effective. Thus, in order to carry out long duration washing at a spinning process, an easy approach uses the Nelson roller.

[0020] In this way, only a predetermined number can bundle the obtained hollow fiber, resin adhesion can be carried out, and a module can be obtained by starting an edge. Optimum dose mixing of tap

water and the reverse osmosis (RO) water was carried out, 5L adjustment of Et liquid of about 3000 EU/L was done, and it put into the beaker, and in order to measure the modular endotoxin amount of adsorption, from the modular dialysing fluid inlet port, Et liquid is introduced by the rate of flow of 500 ml/min, and it filters to the hollow filament inside by filtration flow rate 100 ml/min, and filtrate and dialysing fluid outlet liquid are returned to the original beaker, and were circulated for 2 hours. By measuring the endotoxin concentration in the beaker circulation before and after circulation, the quantum of the amount of endotoxins which stuck to the film can be carried out. The endotoxin amount of adsorption is so desirable that it is high in order to bar endotoxin mixing into blood. The quantum was carried out to measurement of endotoxin concentration by measuring nephelometry time amount in the TOKISHINO meter ET 201 using Wako Pure Chem RIMURUSU ES-II Test Wako.

[0021]

[Example] Although an example is given to below and this invention is explained, this invention is not limited at all.

[0022] Polyether sulphone (PES) a polyvinyl pyrrolidone (K-90) to a hydrophilization agent 17.0% of the weight 3.0 % of the weight, (Example 1) Inner liquid concentration (DMAC+ water) to a solvent water dimethylacetamide (DMAC) 75.0% 5.0% of the weight as a non-solvent as 50% After making into 0.6 seconds, discharge, AG die length of 600mm, and a part for /, i.e., the spinning speed AG residence time of 60m, the outside of the duplex spinneret which kept the spinning undiluted solution at 40 degrees C to inner liquid from the inside of a duplex spinneret, After being immersed to the coagulation bath of 10% of 70-degree C coagulation bath concentration (DMAC+ water), 45 degrees C of pure water wash for 45 seconds at 80 degrees C of pure water for 1 minute, and it rolls round to skein, and it is the bore of 198.2 micrometers. The hollow fiber of 29.4 micrometers of thickness was obtained. The temperature of the AG section in a 250mm part is 45 degrees C from the nozzle at this time, humidity is 95%, and it is thought that the phase separation of an outside surface can be promoted with the moisture of the AG section.

[0023] The outside-surface SEM image (one 10,000 times the scale factor of this) of the obtained hollow fiber is shown in drawing 1 . an outside-surface SEM photograph -- the image analyzer V20 by Toyobo Co., Ltd. -- using -- TOKS -- law -- the image which performed the image processing in binarization is shown in drawing 2 . The outside-surface hole density searched for from now on was 30.1%.

[0024] Fixing of yarn was not observed at all, but while the module assembly was easy, the channeling of dialysing fluid was not seen, but the solute removal engine performance needed as shown in Table 1 was able to be discovered. The module of 2 was assembled 1.5m of film surface products, and when the amount of PVP eluted from a module using an ethanol water solution 40% was measured, it was thought that they were completely satisfactory even if 1.5mg and the amount of those are slight and it uses them by clinical.

[0025] PVP part clothes volume at this time The quantum was carried out in the following ways using 1 H-NMR spectrum and the infrared absorption spectrum.

(1) It is 1 H-NMR spectrum hollow fiber DMSO-d6 It was made to dissolve and 1 H-NMR spectrum was measured at 60 degrees C. measurement -- the product made from Varian -- Unity-500 (at the time of H measurement 500MHz) was used. 1 From the integrated-intensity ratio of the peak (four protons /repeat unit) of the ring origin of the polysulfone system polymer near [in a H-NMR spectrum] 7.2 ppm, and the peak (four protons /repeat unit) of the pyrrolidone ring origin of 1.8-2.2 ppm PVP, the average PVP content Cave in the film (wt%) was computed.

[0026] (2) Infrared absorption spectrum (FT-IR spectrum)

Measurement of the outside surface in the film performed measurement of an ATR method and the whole film with the transmission method. In measurement, it is SPECTRA. Product made from TECH IRmus/SIRM was used. In the ATR method, diamond 45 degree was used as an internal reflection element. the ratio of the absorption intensity Ap of the peak originating in C=O of PVP of 1675cm-1 in an infrared absorption spectrum, and the absorption intensity As of the peak in which the polysulfone system polymer of the 1580cm-1 neighborhood originates -- Ap/As was calculated. since absorption intensity is dependent on the measurement wave number in an ATR method -- as correction value -- the peak location nu of a polysulfone system polymer -- the ratio of peak location nup (wave number) of s and PVP -- nu p/nu s was applied to the actual measurement.

[0027] Internal-surface PVP content (Ci) and the PVP content (Co) of an outside surface were computed from the following formulas.
Ci=CavexRi/Rt (formula 2)
Co=CavexRo/Rt (formula 3)
Cave: PVP content Ri for which it asked from 1 H-NMR: FT-IR PVP of an internal surface and the extinction quotient of a polysulfone system polymer (after amendment) in an ATR method
Ro : FT-IR PVP of an outside surface and the extinction quotient of a polysulfone system polymer (after amendment) in an ATR method
Rt : Extinction quotient of PVP in a FT-IR transmission method, and a polysulfone system polymer
[0028] Film obtained on the above-mentioned spinning conditions 1 H-NMR spectrum is shown in drawing 3 , and an enlarged drawing is shown in drawing 4 . The chart according the chart by the infrared extinction spectrum ATR method to an infrared extinction spectrum transmission method is shown in drawing 5 at drawing 6 . 3.0%, the PVP content of an internal surface and an outside surface is 8.3% and 1.7%, respectively, and the average PVP content Cave for which it asked from these charts was filling the formula 1. The module was obtained by it being filled up with these 9976 hollow filaments to a case, pasting up by resin, and starting an edge with a cutting edge. The modular filling factor was [24.0cm and effective length's film surface product] 2 1.49m 57%. The endotoxin adsorption test was performed using this module.
[0029] That is, it was made to circulate by mixing tap water and Milli Q water using Et liquid of 3160 EU/L by dialysing fluid inlet-port flow rate 500 ml/min and filtration flow rate 100 ml/min. The endotoxin concentration of Et liquid of 2 hours after was 2140 EU/L, and the endotoxin amount of adsorption was 5100EU, and when it was changed to per unit membrane area, it was 3400 EU/m2. In addition, Et concentration of the filtrate under measurement is below limit of detection, and endotoxin mixing was suppressed.
[0030] Polyether sulphone (PES) Polyvinylpyrrolidone K90 (K90) to a hydrophilization agent 17.0% of the weight 3.0 % of the weight, (Example 1 of a comparison) Inner liquid concentration (DMAC+ water) to a solvent water dimethylacetamide (DMAC) 75.0% 5.0% of the weight as a non-solvent as 60% After making into 0.1 seconds, discharge, AG die length of 50mm, and a part for /, i.e., the spinning speed AG residence time of 30m, the outside of the duplex spinneret which kept the spinning undiluted solution at 40 degrees C to inner liquid from the inside of a duplex spinneret, After being immersed to the coagulation bath of 30% of 40-degree C coagulation bath concentration (DMAC+ water), 45 degrees C of pure water washed for 45 seconds at 80 degrees C of pure water for 1 minute, it rolled round to skein, and the hollow fiber of 30 micrometers of thickness was obtained. The temperature of the AG section in a 25mm part was 38 degrees C from the nozzle at this time, and humidity was 80%. The outside-surface SEM image (one 10,000 times the scale factor of this) of the obtained hollow fiber is shown in drawing 7 . An aperture was not seen at all by the outside surface, but it was considered that outside-surface hole density was 0%. When yarn was dried, fixing of yarn was violently impossible for the modularization.
[0031] They are an example 1 and this appearance about the PVP part clothes volume at this time. When the quantum was carried out using 1 H-NMR and FT-IR, the average PVP content in the film was 4.0%. The PVP content of an internal surface and an outside surface was 5.0% and 6.0%, respectively, and there were very many PVP contents of an outside surface.
[0032]
[Table 1]

	実施例1	比較例1
膜厚（μm）	30	30
ノズル温度（℃）	40	40
AG滞留時間（sec）	0．6	0．1
AG部温度（℃）	45	38
AG部湿度（%）	95	80
凝固浴温度（℃）	70	40
外表面開孔率（%）	30．1	0．0
PVP溶出量（mg）	1．5	モジュール組立不可
エンドトキシン吸着量（EU／m²）	3400	モジュール組立不可
膜内の平均PVP含有率（Cave）	3．0	4．0
膜内表面のPVP含有率（Ci）	8．3	5．0
膜外表面のPVP含有率（Co）	1．7	6．0

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DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]
[Drawing 1] The scanning electron microscope photograph (one 10,000 times the scale factor of this) of the outside surface of the hollow fiber obtained in the example 1 is shown.
[Drawing 2] the outside-surface scanning electron microscope photograph of drawing 1 -- the image analyzer V20 by Toyobo Co., Ltd. -- using -- TOKS -- law -- the image which performed the image processing in binarization is shown.
[Drawing 3] Hollow fiber obtained in the example 1 1 H-NMR spectrum is shown.
[Drawing 4] Hollow fiber obtained in the example 1 The enlarged drawing of 1 H-NMR spectrum is shown.
[Drawing 5] The chart by the infrared extinction spectrum ATR method of the hollow fiber obtained in the example 1 is shown.
[Drawing 6] The chart by the infrared extinction spectrum transmission method of the hollow fiber obtained in the example 1 is shown.
[Drawing 7] The scanning electron microscope photograph (one 10,000 times the scale factor of this) of the outside surface of the hollow fiber obtained in the example 1 of a comparison is shown.

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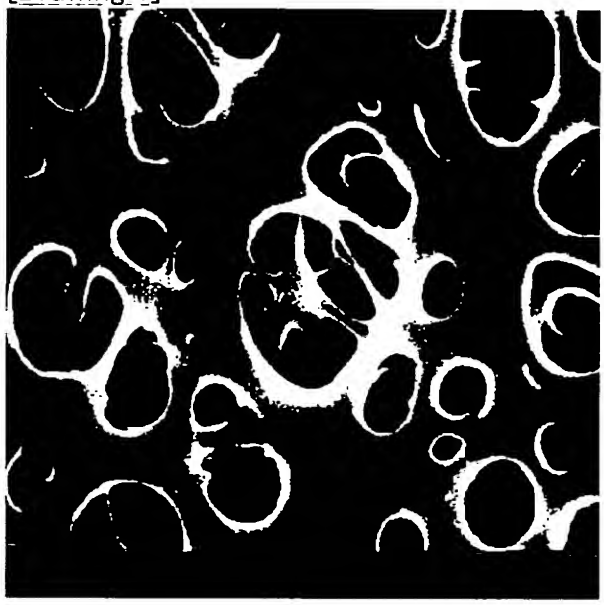
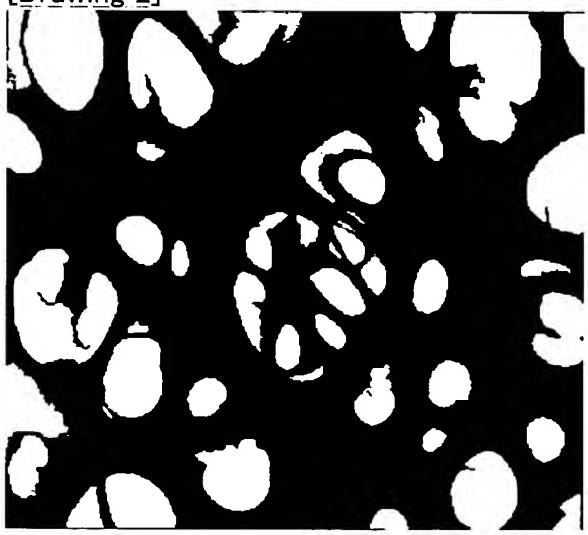
DRAWINGS

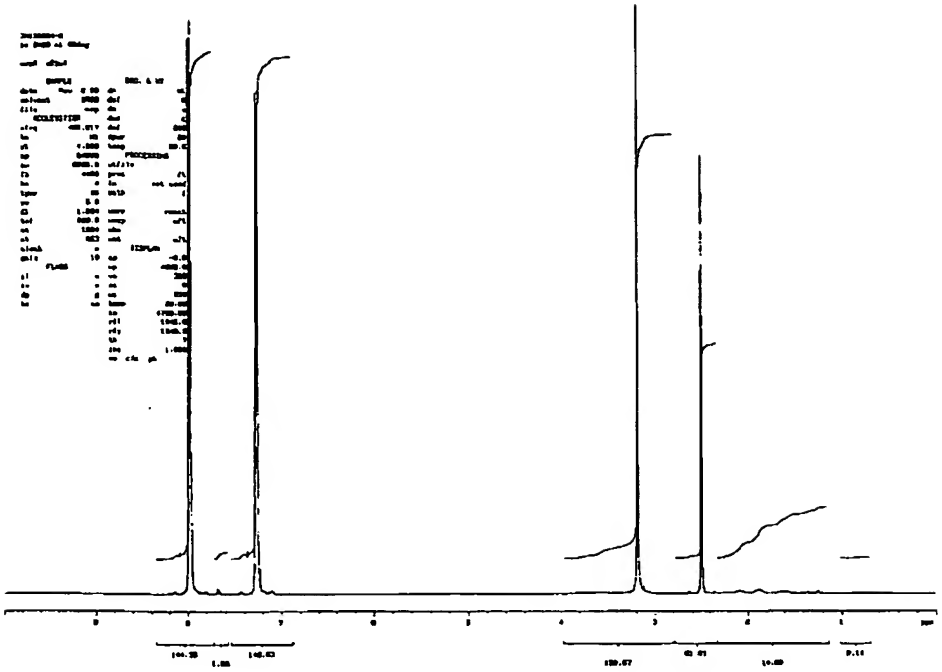
[Drawing 1]



[Drawing 2]



[Drawing 3]



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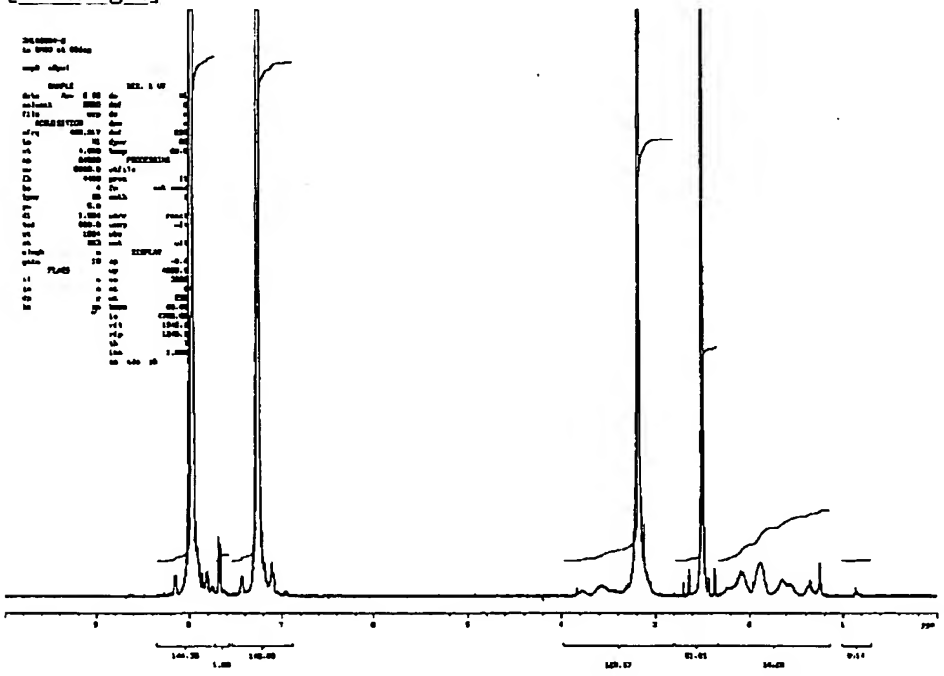

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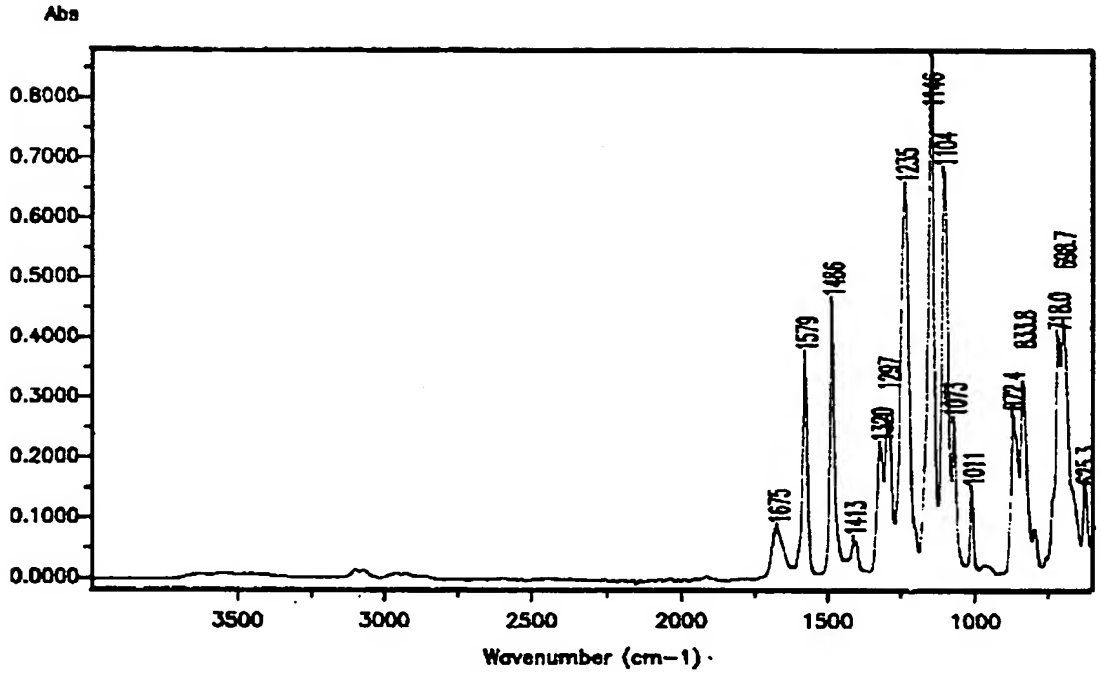
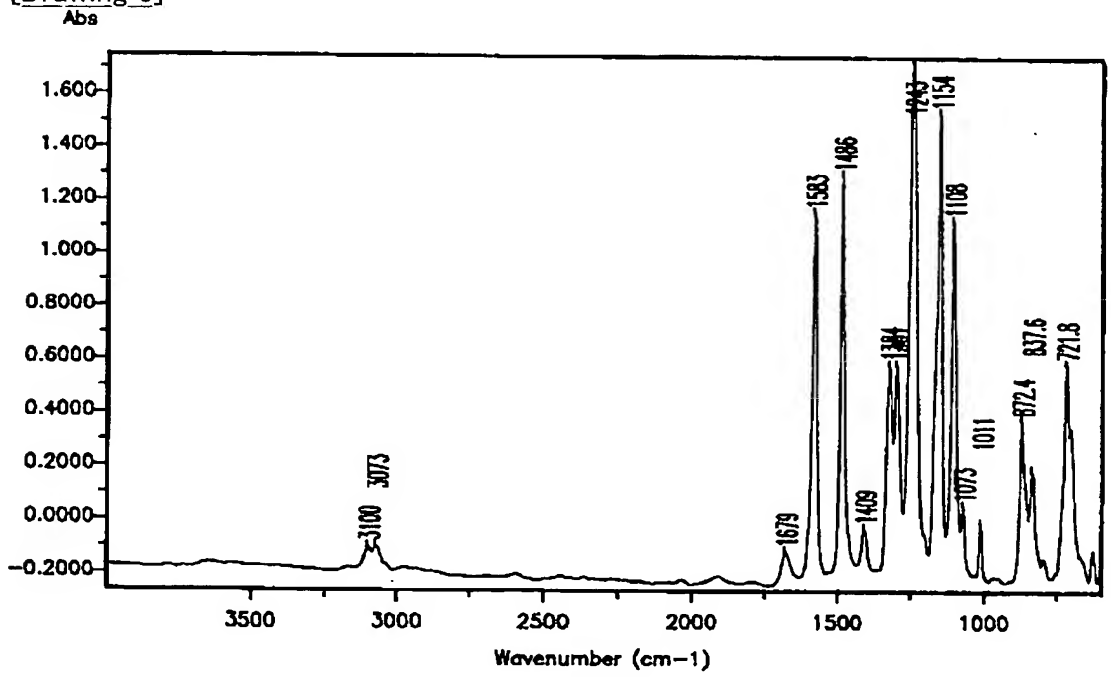
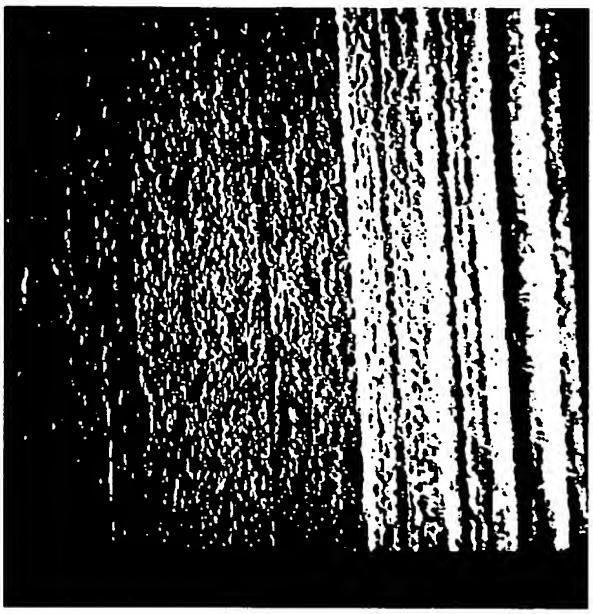


[Drawing 6]



[Drawing 7]



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